2.0 DESCRIPTION OF PROPOSED RESEARCH IN NON-TECHNICAL LANGUAGE

Rheumatoid arthritis (RA) is a chronic disease caused by the body's natural immune system attacking healthy joint tissue for unknown reasons. This causes joint inflammation, which results in joint pain and swelling, and ultimately joint destruction and disability. It is one of the most common chronic inflammatory diseases in the US.

Patients with RA have benefited from new medications such as Enbrel®, Remicade® and Humira®, a new class of therapies that blocks a protein called TNF-α (tumor necrosis factor-alpha). This protein is a key contributor to the inflammation that leads to the joint damage and bone destruction in RA. These medications, which are given by injection under the skin or into the bloodstream, have led to remarkable improvement in the symptoms of RA. However, some RA patients have one or more joints that bother them despite these medications, or only one or two problematic joints, which may demonstrate progressive joint destruction. These patients might benefit from direct injection of genes coding for proteins that block TNF-α into the joint. Injection of genes may be an ideal means of providing therapeutic proteins because it would require less frequent injections, in contrast to direct injection of protein, which requires more frequent injections, since proteins are degraded rapidly in the body.

Targeted Genetics Corporation has developed a special gene carrier, or vector, to help a gene coding for a protein that blocks TNF-α get inside cells. This vector, called tgAAC94, is based on a virus called adeno-associated virus (AAV) and produces the same protein as Enbrel®. Animal tests have shown that tgAAC94 is safe in animal models and that a similar vector especially made for rats also leads to improvement of arthritic joints in a rat model of arthritis. Many people have been infected by the naturally occurring type of AAV without realizing it, as AAV does not cause disease.

Targeted Genetics Corporation proposes to test the safety of tgAAC94 in a study of 32 patients with RA who have persistent swelling in one or more joints despite treatment with strong RA medications. Four groups of 8 patients each will be enrolled and randomly assigned (like the flip of a coin) to a single injection of either tgAAC94 or placebo. The dose of tgAAC94 will be increased between the first three groups.

To expand the safety profile and gather additional information about efficacy, subjects will be enrolled in the fourth group and receive tgAAC94 at the highest dose determined to be safe after review of the safety data from the first three groups. An independent panel of experts will oversee the study and recommend that the study be stopped if safety issues arise.